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PATENT

Attorney Docket No.: 02307O-138220US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Michael German *et al.*

Application No.: 09/811,323

Filed: March 16, 2001

For: DELIVERY OF THERAPEUTIC
GENE PRODUCTS BY
INTESTINAL CELL EXPRESSION

Examiner: Dave Trong Nguyen

Art Unit: 1632

**DECLARATION UNDER
37 C.F.R. § 1.131**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

We, Michael S. German, Associate Professor of Medicine at the University of California, San Francisco (UCSF); Stephen Rothman, Professor of Stomatology and Physiology at UCSF; and Ira D. Goldfine, Professor in Residence of Medicine and Physiology at UCSF, state as follows:

1. We are co-inventors of the invention claimed in U.S. Patent Application No. 09/811,323, filed March 16, 2001 (herein "the '323 Application"), which claims priority to U.S. Patent Application No. 08/717,084, filed September 20, 1996.
2. The invention disclosed and claimed in the '323 Application is directed to, *inter alia*, methods of delivering a secreted protein to the bloodstream by intestinal cell expression of a foreign gene encoding the protein. In one embodiment of our invention, the method comprises the following steps:

introducing into the gastrointestinal tract of a mammalian subject by oral administration a construct which is formulated as a pill, a capsule, or a tablet, said construct comprising

(a) a nucleic acid molecule comprising a coding sequence encoding a protein; and

(b) a promoter sequence operably linked to the coding sequence,

wherein said construct is not packaged in a viral particle, said introducing resulting in introduction of the construct into an intestinal epithelial cell, production of the encoded protein in the intestinal epithelial cell and secretion of the protein from the cell and into the bloodstream of the subject.

In another embodiment, the disclosed and claimed method is directed to the induction of an immune response to a secreted protein antigen, the method comprising the following steps:

introducing into the gastrointestinal tract of a mammalian subject by oral administration a construct comprising

(a) a nucleic acid comprising a coding sequence encoding a secreted protein antigen; and

(b) a promoter operably linked to the coding sequence,

wherein said construct is not packaged in a viral particle, said introducing resulting in introduction of the construct into an intestinal epithelial cell and secretion of the protein antigen from the cell and into the bloodstream of the subject, and wherein an immune response to the protein antigen is induced in the subject.

3. We understand that the pending claims of the '323 Application stand rejected over U.S. Patent No. 6,248,720 to Mathiowitz *et al.* entitled "Method for Gene Therapy Using Nucleic Acid Loaded Polymeric Microparticles) (herein "Mathiowitz"), which issued on June 19, 2001, and was filed on July 3, 1996.
4. Prior to July 3, 1996, we conceived of the invention in the United States. As evidence of our conception of the claimed invention prior to July 3, 1996, we have attached hereto Exhibits A, B, and C.
5. Exhibit A is a copy of a letter, written and signed by Dr. German, to Linda Carloni of the UCSF Office of Technology Transfer. This letter was written and is dated prior to July 3, 1996 (date redacted from copy provided). This letter describes, *inter alia*, our conception of systemic delivery of a secreted protein to the bloodstream via transfection of intestinal epithelial cells with a foreign DNA encoding the protein. This letter further sets forth (a) that such introduction of a gene into gut epithelial cells can be used to induce in the subject an immune response against a secreted protein antigen and (b) that different administration routes (*e.g.*, oral and rectal) can be utilized for introducing the DNA construct into the intestinal lumen.
6. Exhibit B is a copy of a letter, written and signed by Dr. Rothman, to Carol Francis, a patent agent with Fish and Richardson P.C. This letter was written and is dated prior to July 3, 1996 (date redacted from copy provided). This letter refers to materials and narrative requested for the preparation of the '084 Application. Exhibit C is copies of three pages from the referenced narrative, with the heading "Gene Therapy by the Oral Route" (numbered pages 6-8). Exhibit C sets forth that the introduction of a gene into gut epithelial cells for delivery of proteins to the bloodstream, in accordance with our conceived methods, can be achieved by oral administration of "plasmid/vector containing pills."

7. On September 20, 1996, we constructively reduced the invention to practice by filing the '084 Application.
8. Commencing no later than prior to July 3, 1996, and continuing until September 20, 1996, we, directly or through persons acting under our direction and supervision, carried out diligent efforts to reduce the invention to practice. As evidence of our diligent efforts to reduce the invention to practice, we have attached hereto Exhibits D through I.
9. Our work toward reduction to practice included studies of the delivery of human growth hormone (hGH) to the bloodstream by injecting a vector encoding hGH into the intestinal lumen. These experiments were carried out before July 3, 1996. Results from at least one of these studies are described more fully in the '323 Application (*see* Examples 1 and 2).
10. Exhibit D contains true copies of pages from the notebook of Filemon Sorillo Dela Cruz ("Mr. Cruz"), a summer student in Dr. German's lab during the summer of 1996. Mr. Cruz's work involved the construction of a Green Fluorescence Protein ("GFP") vector for additional *in vivo* studies. Our goal was to use the GFP vector to confirm, as well as to precisely track, intestinal cell expression of a construct delivered to the intestinal lumen. Exhibit D shows that Mr. Cruz performed work on construction of the GFP vector commencing no later than July 1, 1996, and continuing at least until August 25, 1996, when Mr. Cruz returned to school for the Fall Semester at Reed College in Oregon. Exhibit D further shows that the following work was conducted:
 - (1) Construction of pFOXEGFP-N1: July 1-3 and July 5, 1996;
 - (2) Restriction analysis of pFOXEGFP-N1: July 5 and July 8, 1996;
 - (3) Reculture, miniprep, and restriction analysis of pFOXEGFP-N1 colony 24: July 8 and July 9, 1996;

- (4) Ligation of pFOXEGFP-N1 with human β -globin intron: July 9 and July 10, 1996;
- (5) Sequence analysis of pFOXEGFP-N1: July 10, 1996;
- (6) Restriction analysis of primary plasmids used to construct GFP plasmid: July 11 and July 12, 1996;
- (7) Ligation of cut pEGFP-C1 and MG528/MG529 oligonucleotides: July 12-13 and July 15, 1996;
- (8) Restriction analysis of DNA minipreps from cultured cells containing ligation of pEGFP-C1 and MG528/MG529 oligos: July 16-18 and August 5-8, 1996;
- (9) Ligation of pFOXSB and 750 bp fragment of pEGF-N: August 8, 1996;
- (10) Ligation of pEGFP-N1 with human β -globin intron: August 11-15, 1996;
- (11) Restriction analysis of DNA minipreps from cultured cells containing ligation of pEGFP-N1 with human β -globin intron: August 16 and August 19-20, 1996; and
- (12) Ligation of pEGFP-N2 with 750 bp fragment of pFC2 -482 rglc Z: August 21-25, 1996.

11. In addition to our studies in the lab, we worked with Carol Francis of Fish and Richardson to diligently prepare the '084 Application commencing no later than July, 1996, and continuing until September 20, 1996. (*See Exhibits E through I.*)
12. Exhibit E is a copy of a letter, written and signed by Carol Francis, to Dr. Rothman. The letter is dated August 8, 1996. This letter refers to a revised draft of the '084 Application (herein "the revised draft"), forwarded with the letter, and further sets

forth that the revised draft incorporated comments from Dr. Rothman communicated to Carol Francis by letter on July 29, 1996. This letter also confirms, *inter alia*, that a draft application prepared by Carol Francis had been reviewed by Dr. Rothman during the period prior to July 29, 1996.

13. Exhibit F is a copy of a letter, written and signed by Dr. Rothman, to Carol Francis. The letter is dated August 13, 1996. This letter communicates Dr. Rothman's comments regarding the revised draft. This letter confirms that Dr. Rothman reviewed and noted comments regarding the revised draft during the period between August 8 and August 13, 1996.
14. Exhibit G is a copy of a letter, written and signed by Carol Francis, to Dr. German. The letter is dated August 13, 1996. This letter sets forth, *inter alia*, Carol Francis's plan to further revise the draft application according to the comments provided in Dr. Rothman's letter of August 13, 1996 (Exhibit F) as well as data provided by Dr. Rothman in a letter dated August 8, 1996.
15. Exhibit H is a copy of an invoice from Fish and Richardson P.C. for services provided in the preparation of the '084 Application (*see* Exhibit I, "Declaration of Andrea Eubanks Under 37 C.F.R. § 1.132"). We have reviewed Exhibit H. We believe that Exhibit H, in addition to further confirming the facts set forth in ¶¶11-13, *supra*, confirms the following:
 - (1) correspondence from Dr. Rothman regarding the revised draft was reviewed on August 20 and the draft application was further revised to incorporate Dr. Rothman's comments (herein the "new draft");
 - (2) correspondence to us regarding the new draft was being prepared on August 20, 1996;

(3) The new draft was further reviewed on August 27 and forwarded to us with a letter; and

(4) as of August 27, 1996, work was being performed on the IDS to file with the application.

16. We further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that we make these statements with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of any patent issuing from U.S. Patent Application No. 09/811,323.

Date: _____

Michael S. German

Date: _____

Stephen Rothman

Date: _____

Ira Goldfine